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A Convenient Road to 1-Chloropentacycloundecanes – A Joint Experimental and Computational Investigation

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An efficient synthetic strategy to obtain 1-chloro-C_s-trishomocubane and 1-chloro-D_3-trishomocubane is described. 1-Chloro-C_s-trishomocubane is synthesized by a regioselective Diels–Alder reaction, and B3PW91/6-31G(d,p) calculations offer a plausible explanation of the reaction mechanism. Surprisingly, 1-chloro-C_s-trishomocubane does not undergo an acid-catalyzed rearrangement to form 1-chloro-D_3-trishomocubane and was obtained by chlorosulfation of Cookson's diketone. A possible mechanism of the reaction involving the formation of C_s- and D_3-trishomocubane nonclassical cations was proposed on the basis of a mechanistic [B3PW91/6-31G(d,p) and MP2/cc-pVDZ] study.

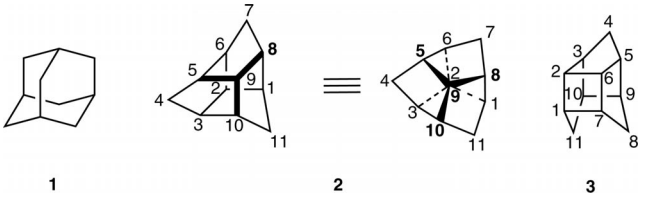
Introduction

Polycyclic cage compounds have been drawing the attention of organic chemists since the middle of the last century. Interest in the pharmacology of polycyclic cage amines was stimulated by early findings that adamantane amine, 1-amino-adamantane or amantadine, had antiviral activity against a variety of viruses, including influenza,[1,2] hepatitis C[3,4] and herpes zoster neuralgia.[5,6] Amantadine is a specific inhibitor of the M2 ion channel of the influenza virus and is believed to form a hydrogen bond with a histidine residue (His-37) in the M2 protein, effectively blocking the ion channel.[7]

Interest in the pharmacology of polycyclic cage compounds was further stimulated when a variety of adamantane derivatives with a wide range of pharmacological properties were synthesized. Adamantane is found in different drugs [memantine,[8] remantadine,[9] midantane[10] and adapromine[11] (drugs against flu, tick-borne encephalitis, CNS diseases), gludantan,[12] bemantane[13] and himantan[14] (Parkinson's disease), dimantane (CNS disease) and kemantane[15] (HIV and chronic fatigue syndrome)]. Evidently the polycyclic cage is useful both as a scaffold for sidechain attachment and to improve drug lipophilicity. Additionally, polycyclic cage compounds can be used as polymeric compounds,[16–19] polymer materials[20] and thermostable oils.[21,22] Also under active investigation is possibility to use polymantanes in the nanoworld.[23]

In general, the bioactivity profile of polycyclic cage compounds can be effectively manipulated by means of structural modification, either within the polycyclic cage moiety or by sidechain substitution. It was recently suggested that, "the polycyclic cage structure seems to be ideally suited for developing multiple mechanism drugs, as it can both serve as a scaffold for the drug molecule proper, or as a moiety that may be added to improve the pharmacokinetic properties of drugs currently used in the clinic, or drug candidates under development."[24]

Both, adamantane (**1**) (T_d symmetry) and D_3-symmetrical trishomocubane, pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane (**2**), have a relatively large hydrocarbon cage size (ca. 5.5 Å), high lipophilicity and are conformationally rigid. The last two properties are particularly very important for drugs. Additionally, they both are stabilomers (the most thermodynamically stable of all possible isomeric $C_{10}H_{16}$ and $C_{11}H_{14}$, respectively).



1 **2** **3**

Although **2** was synthesized in 1970,[25] to date there have been less than 100 articles published on the synthesis and reactivity of D_3-trishomocubane and its derivatives.[26] It is also one of the symmetrical cage hydrocarbons that has planar chirality. Hence, its optical activity offers capabilities inaccessible to most other cage compounds, allowing **2** to find application virtually everywhere adamantane derivatives are used.

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Nonetheless, derivatives of **2** remain virtually unexplored. The reasons for this are limited synthetic methods, harsh reaction conditions, and often unsatisfactory yields of the desired D_3-trishomocubane derivatives. The majority of synthetic routes to **2** and its derivatives are based on rearrangements of the carbon cage of isomeric cage structures, usually pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (C_s-trishomocubane, **3**).

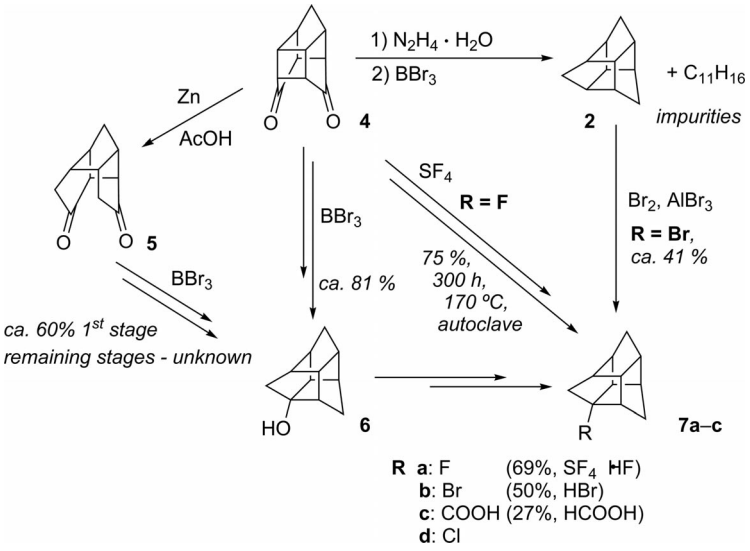
While C^4 derivatives of D_3-trishomocubanes are the most studied, tertiary C^1 and C^2 substituted precursors (hydroxo-, halo-, etc.) are difficult to synthesize. There are few synthetic routes that yield 1-substituted D_3-trishomocubane and none can be regarded as preparative.

The most popular technique used to synthesize substituted compounds is to use chemical methods to modify functional groups on a skeleton (Scheme 1).

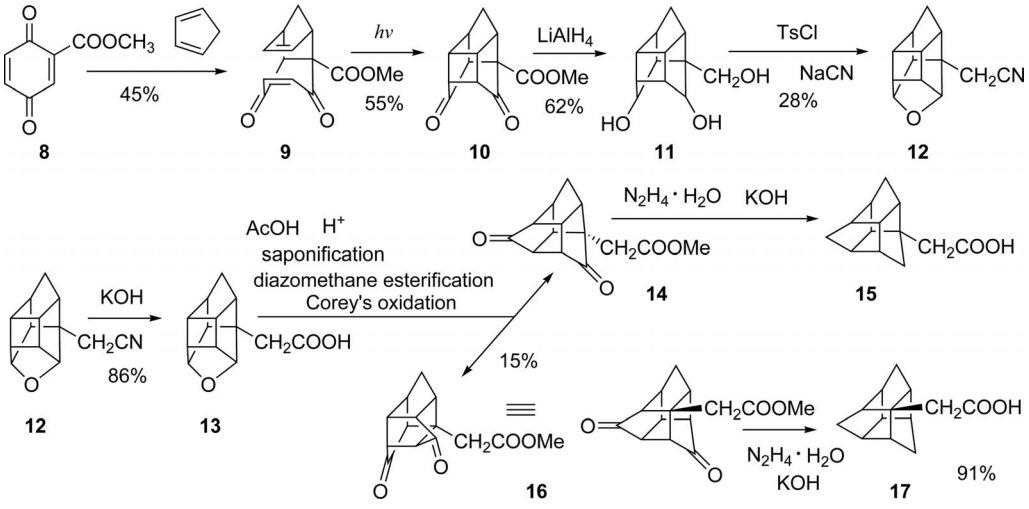
Kukhar and coworkers[27–30] and Kent[31] have synthesized a number of 1-substituted D_3-trishomocubanes [1-hydroxy- (**6**), 1-fluoro- (**7a**), 1-bromo- (**7b**), 1-carboxy- (**7c**)] from **2**, Cookson's diketone **4**, and tetracyclo[6.3.0.0^{4,11}.0^{5,9}]-undecane-2,7-dione (**5**), usually in harsh environments or with low yields (Scheme 1).

Although it is possible to synthesize various precursors (i.e. **6**, **7a**–**c**, Scheme 1) by substitution reactions, the main difficulty is the introduction of a substituent into the C^1-position of **2**.

Both **4** and **5** can be easily synthesized by Diels–Alder reactions. Consequently, another method to synthesize 1-functionalized D_3-trishomocubane is to start with appropriately substituted precursors for the Diels–Alder reaction. Previously reported by Nakazaki,[32] 1-functionalized D_3-trishomocubane **15** was synthesized by the isomerization of monosubstituted Cookson's diketone **10** according to Scheme 2. Unfortunately, formation of the 2-substituted derivative **17** as a side product takes place.



Scheme 1. General scheme for the synthesis of 1-substituted D_3-trishomocubanes. Only the main structures are noted. Conditions and reagents are shown for the main step of each reaction when the trishomocubane structure is formed.



Scheme 2. Synthesis of (1-D_3-trishomocubyl)- (**15**) and (2-D_3-trishomocubyl)- (**17**) acetic acids.

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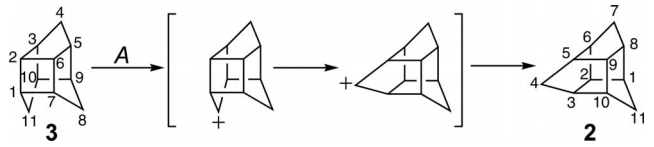
Thus, we have developed an efficient route to 1-substituted D_3-trishomocubanes.

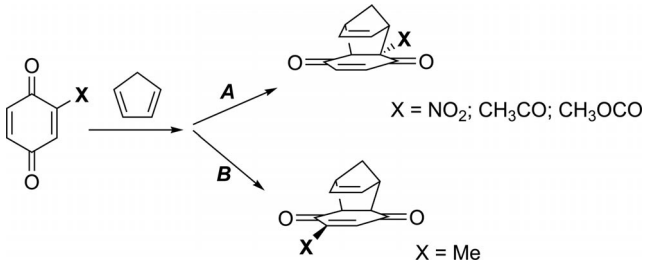
Results and Discussion

It is known that under acidic conditions or Lewis acid catalysis, C_s-trishomocubane **3** usually undergoes skeleton isomerization into a D_3-cage. This is believed to proceed through the formation of the C_s-trishomocubane C^8 (or equivalent C^{11}) cation, followed by a 1,2-shift, and formation of the D_3-trishomocubane C^4 cation (Scheme 3).[31] Thus, we decided to introduce a chlorine atom into the C^1 position of C_s-trishomocubane and then pursue rearrangement in an acidic environment. Moreover, despite the variety of C_s-trishomocubane derivatives, to the best of our knowledge C^1-substituted C_s-trishomocubane and 1-chloro-D_3-trishomocubane have not been reported.



Scheme 3. Proposed rearrangement pathway from C_s-trishomocubane to D_3-trishomocubane.

The Diels–Alder reaction between cyclopentadiene and quinones followed by intramolecular photocyclization leads to the formation of the C_s-trishomocubane skeleton. The *endo* adduct is usually favoured, and in the case of substituted quinones, reaction with either substituted or unsubstituted double bonds are possible. For example, 2-nitroquinone,[33] 2-acetylquinone[34] and 2-carbometoxyquinone[35] react with cyclopentadiene by a substituted double bond

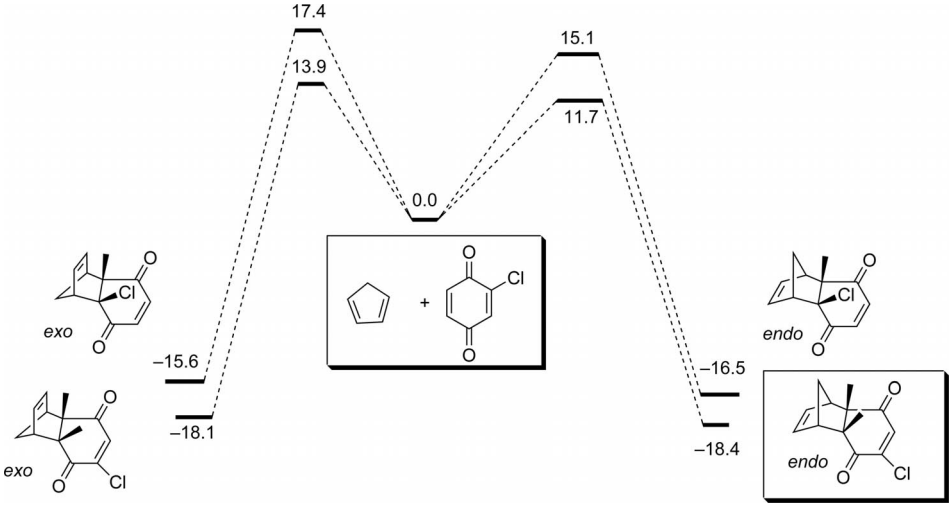


Scheme 4. Adducts of the Diels–Alder reaction of cyclopentadiene with 2-substituted-1,4-quinones.

leading to the adduct according to pathway A (Scheme 4). 2-Methylquinone was reported to give the adduct that results from reaction with an unsubstituted double bond (pathway B, Scheme 4).

Our calculations[36] (Scheme 5) suggest that the Diels–Alder reaction of 2-chloro-1,4-quinone with cyclopentadiene should proceed as an inverse Diels–Alder reaction. Formation of the adduct formed through pathway B is more favourable (both kinetically and thermodynamically) over that formed by pathway A (Schemes 4 and 5). The lowest activation barrier is found to be 11.7 kcal mol^{-1} and the corresponding transition state describes formation of the *endo*-adduct formed through pathway B (Scheme 4).

Thus, in order to introduce a chlorine atom into the pentacycloundecane cage we have used a Diels–Alder reaction between cyclopentadiene and 2-chloro-1,4-quinone. In the first step of the reaction, 2-chloroquinone (**20**, 90% yield) is formed according to Scheme 6. The Diels–Alder reaction of **20** with cyclopentadiene afforded the sole isolable product **21** (77% yield), which gives 1-chloropentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**22**) upon photocyclization. Reduction of **22** with hydrazine hydrate affords 1-chloropentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**23**) in 50% yield (Scheme 6).



Scheme 5. Energy diagram of Diels–Alder reaction of cyclopentadiene with 2-chloro-1,4-quinone [energies are given in kcal mol^{-1}, B3PW91/6-31G(d,p)].

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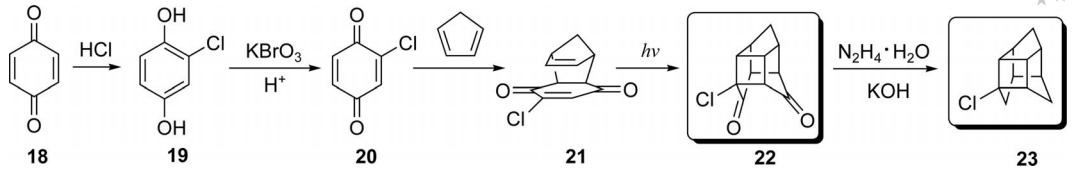

Scheme 6. Synthesis of 1-chloro-C_s-trishomocubane **23**.

Table 1. Relative stabilities of cations **3a**$^+$–**3f**$^+$ and **2a**$^+$–**2c**$^+$ (–E + ZPE, kcal mol^{-1}, relative to **3e**$^+$).

	3	**3a**$^+$	**3b**$^+$	**3c**$^+$	**3d**$^+$	**3e**$^+$	**3f**$^+$
B3PW91/6-31G(d)		7.8	9.0	11.1	8.6	0.0	3.6
B3PW91/6-311+G(d,p)		8.4	9.8	11.7	9.2	0.0	4.2
MP2/cc-pVDZ		13.0	14.6	17.1	12.2 (TS)	0.0	8.9
	2	$^+C^1 = {}^+C^3 = {}^+C^6$ **2a**$^+$		$^+C^2 = {}^+C^9$ **2b**$^+$		$^+C^4 = {}^+C^7 = {}^+C^{11}$ **2c**$^+$	
B3PW91/6-31G(d)		–1.2		5.6		0.0	
B3PW91/6-311+G(d,p)		–0.9		6.1		0.0	
MP2/cc-pVDZ		–0.8		7.9		0.0	

As mentioned above, under acidic conditions 1-chloro-C_s-trishomocubane **23** should undergo rearrangement to form 1-chloro-D_3-trishomocubane. Hydride abstraction from **3** leads to the formation of six possible cations (**3a**$^+$–**3f**$^+$, Table 1 and Figure S1) and, in the case of **2**, to three cations (**2a**$^+$–**2c**$^+$, Table 1 and Figure S1).

As implied by our calculations (Table 1) the $^+C^8$ cation (**3e**$^+$) is most stable. The other C_s-trishomocubane cations in the series are less stable [B3PW91/6-311+G(d,p) +ZPE]: $^+C^8$ (**3e**$^+$, 0.0) < $^+C^9$ (**3f**$^+$, 4.2) < $^+C^1$ (**3a**$^+$, 8.4) < $^+C^4$ (**3d**$^+$, 9.2) < $^+C^2$ (**3b**$^+$, 9.8) < $^+C^3$ (**3c**$^+$, 11.7). At the MP2/cc-pVDZ level the trend is similar; however, the $^+C^4$ cation (**3d**$^+$) is a transition structure between two **3c**$^+$ cations. The **2a**$^+$ and **2c**$^+$ cations are predicted to be isoergic, and the C_3-symmetric cation **2b**$^+$ lies above **2c**$^+$ by 7.9 kcal mol^{-1} (Table 1 and Figure S1).

Careful inspection of the geometry of cation **3e**$^+$ revealed that it is equivalent to **2c**$^+$ (Figure 1 and Table 1). It also should be noted that this process is not a 1,2-hydrogen shift, as proposed earlier (Scheme 3), rather a 1,2-alkyl shift. Therefore, acidic rearrangement of **3** should readily give a derivative with a D_3-moiety.

It is worth noting that of nine possible cations all except **2b**$^+$ and **3f**$^+$ (Figure S1) have closed C–C–C 3c–2e bonds,[37] and are thus nonclassical cations.[38]

Consequently, we have attempted to access the C^1-derivative of **2** by a different route: through the 1-substituted Cookson's diketone. We have modified Kent's[31] synthetic procedure by substituting $AlCl_3$ into CCl_4/CH_2Cl_2. Cage rearrangement does not take place under these conditions

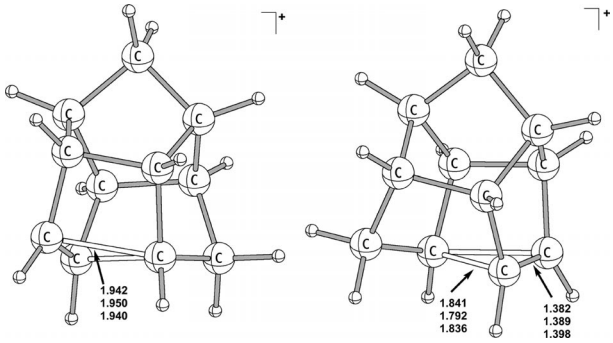

Figure 1. Geometry of cation **3e**$^+$, which is equivalent to cation **2c**$^+$ [bond lengths in Å, B3PW91/6-31G(d) (first entry), B3PW91/6-311+G(d,p) (second entry) and MP2/cc-pVDZ (third entry)].

and 1-chloro-D_3-trishomocubane is not formed. NMR and GS/MS spectra confirm the presence of unreacted **23** only.

This unexpected result prompted us to look for another way to obtain 1-chloro-D_3-trishomocubane. Thus we have modified a method that uses chlorosulfation of diketones and leads to the insertion of a chlorine atom.[39] The first step of the reaction is the chlorosulfation of Cookson's diketone **4** (Scheme 7). This was performed in $CHCl_3$, as opposed to the conditions used previously (HSO_3Cl), for a few hours (increasing the reaction time up to a few days increases yield only by a few%). Under these conditions 1-chloro-11-chlorosulfapentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-7-one (**24**) and 1,11-dichloro[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undec-

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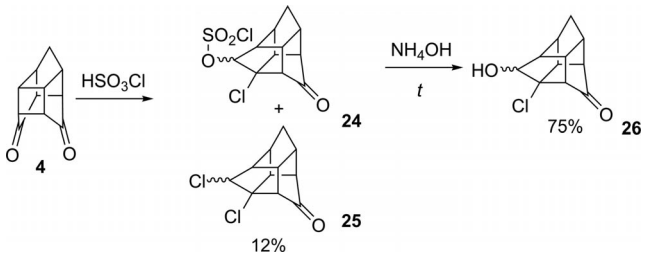
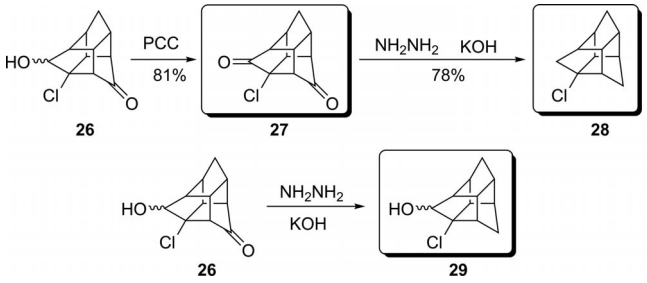
ane-7-one (**25**) are obtained (Scheme 7). Chlorosulfate **24** can be easily hydrolyzed to chloro ketol **26** by boiling in solution of aqueous ammonia. The total yield of **26** from two steps is 75%. A yield of 64% was reported by Tolstikov et al. in the original work.[39] The reaction product contains up to 12% admixture of 1,11-dichloro[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-7-one (**25**), which can be separated chromatographically on Al_2O_3.



Scheme 7. Chlorosulfation of Cookson's diketone **4**.

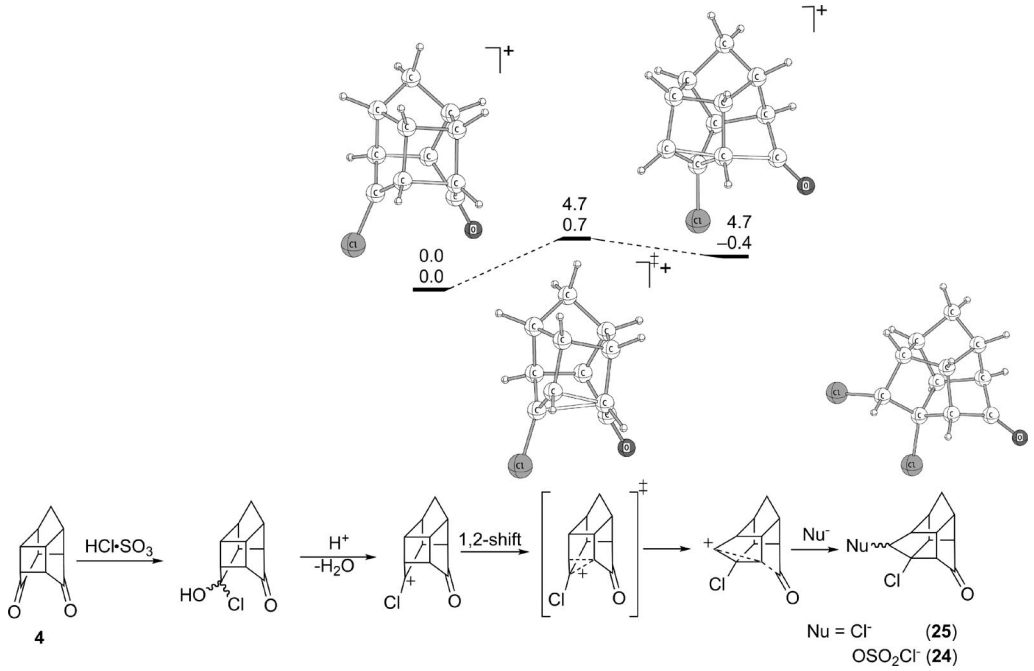
The proposed mechanism of the chlorosulfation of Cookson's diketone **4** is summarized in Scheme 8. The first step is the reaction of one of the keto groups with HCl. Further protonation and the release of water leads to 8-chloropentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-11-one. This cation can easily [ΔE_{act} = +4.7 kcal mol^{-1} and +0.7 kcal mol^{-1}, B3PW91/6-31G(d,p) and MP2/cc-pVDZ, respectively] undergo skeleton rearrangement to form a nonclassical cation with a D_3-trishomocubane structure. This cation can further react with SO_2Cl^- and Cl^- to form **24** and **25**, respectively.

The oxidation of chloro ketol **26**, which gives 1-chloropentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-7,11-dione (**27**) (Scheme 9) was attempted with different oxidizing agents. Oxidation with Jones reagent, CrO_3/acetic acid and $KMnO_4$/acetonitrile/water, leads to a low conversion. Furthermore, with the increase of temperature or time, the yield of byproducts also increases. The best yields (81%) for the oxidation of **26** were obtained using pyridinium chlorochromate (PCC). The results of oxidation are summarized in Table 2.



Scheme 9. Synthesis of 1-chloro-D_3-trishomocubane (**28**) and 1-chloro-D_3-trishomocubane-11-ol (**29**).

A Wolff–Kishner reaction of **27** affords 1-chloro-D_3-trishomocubane (**28**) in 78% yield. It should be noted that in the course of the reaction a white solid sublimes in the reflux condenser. The same reaction with the chloro diketone containing a mixture of nonoxidized chloro ketol **26** affords 1-chloro-D_3-trishomocubane-11-ol (**29**) (75% yield). In this case, after sublimation of **28**, **29** can be easily extracted from the aqueous layer of the reaction mixture into chloroform.



Scheme 8. Plausible reaction pathway of the chlorosulfation of Cookson's diketone **4** [B3PW91/6-31G(d,p) and MP2/cc-pVDZ, –E + ZPE, kcal mol^{-1}].

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Table 2. Oxidation of 1-chloro-11-hydroxypentacyclo-[6.3.0.0^{2,6}.0^{3,1}0.0^{5,9}]undecane-7-one (**26**).

Oxidizing agent	Temp. [°C]	Time [h]	% Yield of **27**	% Yield of **26**	% Yield of byproducts
Jones reagent	20	2	15	48	37
	20	10	24	31	45
	20	40	38	8	54
	30	6	35	11	54
CrO_3, acetic acid	20	10	30	52	18
	20	20	51	19	30
$KMnO_4$, acetonitrile/water	20	10	5	95	–
	20	40	24	68	8
PCC, dichloromethane	40	10	72	18	10
	40	18	81	7	12
	40	40	79	2	19

Conclusions

In summary, we have developed an efficient method to obtain 1-chloropentacycloundecanes through simple transformations, involving Diels–Alder reactions and the chlorosulfation of Cookson's diketone. Previously unknown 1-chloro-D_3-trishomocubane and other derivatives of D_3-trishomocubane have been synthesized. A possible reaction mechanism has been proposed on the basis of mechanistic studies. Due to the availability of the starting materials, mild reaction conditions and potential of the products, this method may be useful in organic synthesis, materials science and medicinal chemistry.

Computational Methods

Geometries were optimized at the MP2[40,41]/cc-pVDZ,[42] B3PW91[43–47]/6-31G(d,p)[48–52] and B3PW91/6-311+G(d,p) levels of theory including frequency analyses to disclose the nature of the stationary points (Nimag = 0 for minima and Nimag = 1 for transition structures) as implemented in the Gaussian 09 program package.[53] Relative energies are Zero Point Energy (ZPE) corrected at all levels. The reaction pathways along both directions from the transition structures were followed by the IRC method.[54]

Experimental Section

General: ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectroscopy measurements were carried out with a Bruker Avance 500 MHz spectrometer; solvent: $CDCl_3$, internal standard: tetramethylsilane (TMS). ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million downfield from TMS. Mass spectroscopy was carried out with an Agilent 5890 Series II 5972 GC–MS spectrometer.

Pyridinium Chlorchromate (PCC): PCC was prepared according to a literature method.[55] The addition of chromium(VI) oxide (25 g, 0.25 mol) to hydrochloric acid (6 N, 46 mL, 0.28 mol) gives the unstable chlorochromic acid. Subsequent addition of pyridine (19.7 g, 0.25 mol) at 0 °C immediately gave pyridinium chlorochromate as yellow-orange solid (45 g, 84%).

Pentacyclo[5.4.0.0^{2,6}.0^{3,1}0.0^{5,9}]-undecane-8,11-dione (4): Pentacyclo[5.4.0.0^{2,6}.0^{3,1}0.0^{5,9}]-undecane-8,11-dione was prepared according to a literature method,[56] which uses the Diels–Alder reaction of *p*-benzoquinone and cyclopentadiene to yield *endo*-tricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-3,6-dione. Irradiation (low-pressure mercury UV lamp, 300 W) of the diene-dione in ethyl acetate gave **4** in 90% yield; m.p. 240.0–242.0 °C, ref.[56] 245 °C. ^{1}H NMR (500 MHz): δ = 2.6–3.3 (m, 8 H), 1.9–2.0 (m, 2 H) ppm. GC–MS (τ = 8.277): *m*/*z* (%) = 174.00 (100), 117.00 (92.96), 91.05 (44.14), 118.00 (35.68), 66.05 (35.01).

***p*-Benzoquinone (18), 2-Chloro-hydroquinone (19) and 2-Chloro-1,4-quinone (20):** Compounds **18**, **19** and **20** were prepared according to literature methods.[57–59]

4-Chloro-tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione (21): To a solution of **20** (30 g, 0.21 mol) ethanol (100 mL) was added cyclopentadiene (17.5 mL, 13.86 g, 0.21 mol) dropwise under constant stirring and cooling. From the pink solution the product precipitated as white crystals, which were collected by filtration and washed with ethanol; yield 38.8 g (90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (m, 2 H), 3.31 (m, 2 H), 3.52 (m, 2 H), 6.06 (s, 2 H), 6.84 (s, 1 H) ppm.

1-Chloropentacyclo[5.4.0.0^{2,6}.0^{3,1}0.0^{5,9}]undeca-8,11-dione (22): Irradiation of 1-chlorotricyclo[6.2.1.0^{2,7}]undeca-8,11-dione (**21**) was carried out in a reaction vessel fitted with a quartz immersion well with a medium pressure mercury vapour lamp (300 W). The reaction was carried out on a solution of **21** (20 g) in dry ethyl acetate (500 mL). The reaction mixture was purged with argon for five minutes and irradiated for 48 h at room temperature under constant argon purging. After evaporation of the solvent and column chromatography (Al_2O_3 column; eluent: CH_2Cl_2) Compound **22** was obtained as white crystals (17.4 g, 87%); m.p. 86.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.02 (q, 2 H), 2.86 (m, 3 H), 2.96 (m, 3 H), 3.30 (m, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 36.98, 41.06 (secondary), 43.72, 44.06, 49.81, 51.44, 54.28, 54.59, 64.76 (quaternary, CCl), 204.15, 208.06 ppm. GC–MS (τ = 11.239): *m*/*z* (%) = 208 (97.109); (τ = 11.838): *m*/*z* (%) 252 (2.891).

1-Chloropentacyclo[5.4.0.0^{2,6}.0^{3,1}0.0^{5,9}]undecane (23): To **22** (1.04 g) was added a 10-fold molar excess of hydrazine hydrate (2.5 g) and diethylene glycol (8 mL). After 8 h of constant stirring at 135 °C, KOH (1.4 g) was added and the temperature was gradually increased. 1-chloro-C_s-trishomocubane **23** sublimed as a white solid in the reflux condenser. The product was dissolved from the condenser with ethyl ether; yield 0.68 g (76%). GC–MS (τ = 8.141): *m*/*z* (%) = 180 (100). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.171 (dt, 1 H), 1.250 (d, 1 H), 1.475 (dd, 1 H), 1.645 (d, 1 H), 1.699 (d, 1 H), 1.840 (d, 1 H), 2.200–2.300 (m, 2 H), 2.329 (m, 1 H), 2.434 (s, 1 H), 2.687–2.920 (m, 2 H), 2.849 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.08, 34.20, 36.25 (secondary), 40.29, 40.50, 41.54, 45.82, 45.89, 48.78, 53.76 (tertiary), 69.40 (quaternary) ppm.

Isomerization of 1-Chloropentacyclo[5.4.0.0^{2,6}.0^{3,1}0.0^{5,9}]undecane (23): Aluminium chloride (two to three times the weight of the hydrocarbon) was added to a carbon tetrachloride solution of **23**. The reaction mixture was stirred at room temperature for 2 h and then poured on to ice. The organic phase was separated and dried with anhydrous magnesium sulfate before the solvent was removed. Only unreacted **23** was isolated, which was confirmed by GC–MS and NMR spectra.

Reaction of Cookson's Diketone (4) with Chlorosulfonic Acid: Chlorosulfonic acid (94 mL, 1.43 mol) was added dropwise to a cold stirred solution of **4** (50 g, 0.287 mol) in chloroform (400 mL) and the mixture immediately turned black. After 24 h of stirring, the reaction mixture was poured into ice. The chloroform was separated and the aqueous phase was washed with chloroform. The

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combined chloroform phases were washed with water until the pH = 6. After drying with anhydrous Na_2SO_4 the solvent was removed to obtain the product as a yellow solid (75 g). GC–MS: **4** 1.55%, **24** 69.91%, **25** 12.51%, **26** 16.02%. GC–MS (**24**) (τ = 10.730): *m*/*z* (%) = 66.05 (100), 129.00 (36.13), 115.15 (28.79), 39.05 (21.06), 117.00 (19.54).

1-Chloro-11-hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,1}0.0^{5,9}]undecane-7-one (26): To the mixture obtained from the reaction of 4 with chlorosulfonic acid as described above (40 g) was added ammonia solution (25%, 800 mL). The reaction mixture was heated under reflux for 2 h, extracted into chloroform, dried and filtered. A brown amorphous substance (25 g) was obtained after evaporation of the solvent. The products were separated with column chromatography on Al_2O_3. Elution with 10% ethyl acetate/hexane on gave dichloro ketone **25** as a white solid. Chloro ketol **26** was eluted from the chromatographic column with methanol. After evaporation of methanol **26** (23.8 g) was obtained as a white solid. GC–MS: **25** 11.5%, **26** 88.5%. **26**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.64 (s, 2 H), 2.08 (d, 2 H), 2.33 (s, 1 H), 2.53 (m, 4 H), 3.22 (s, 1 H), 4.07 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.29, 36.48, 38.82, 45.39, 47.08, 48.51, 49.33, 50.54, 71.51, 77.52, 210.91 ppm. GC–MS (τ = 8.886): *m*/*z* (%) = 66.05 (100), 82.05 (66.47), 39.05 (58.49), 129.00 (58.23), 116.00 (49.95). **25**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 2 H), 2.13 (m, 2 H), 2.56 (s, 4 H), 3.25 (s, 1 H), 4.14 (s, 1 H) ppm. GC–MS (τ = 9.033): *m*/*z* (%) = 66.05 (100), 129.00 (49.42), 128.10 (33.38), 228.00 (30.99), 133.95 (28.91).

1-Chloro-*D*$_3$-pentacyclo[6.3.0.0^{2,6}.0^{3,1}0.0^{5,9}]undecane-7,11-dione (27): To a solution of chloro ketol **26** (9 g, 0.043 mol) in dichloromethane (60 mL) was added a suspension of PCC (13.5 g. 0.065 mol) in dichloromethane (60 mL). The reaction mixture was heated to reflux with stirring for 18 h. The orange mixture turns brown after one hour and black after three hours. Dry diethyl ether (50 mL) was added and the suspension was decanted. The insoluble residue was washed three times with several portions of ether (20 mL). The combined organic solution was filtered through Al_2O_3, and the solvent was removed by distillation to yield **27** as a white solid (7.23 g, 81%). GC–MS: **27** 98.3%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.046–1.47 (m, 2 H), 1.47–2.00 (m, 3 H), 2,00–2.60 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.09, 37.70, 40.69, 42.60, 44.71, 47.29, 47.51, 47.84, 64.13, 203.06, 207.19 ppm. GC–MS (τ = 8.886): *m*/*z* (%) = 117.15 (100), 208.00 (78.75), 115.15 (46.5), 145.05 (39.4), 180.10 (31.64).

1-Chloro-*D*$_3$-trishomocubane (28): Chloro diketone **27** (6.25 g, 0.03 mol) and hydrazine hydrate (15 g, 0.3 mol) were stirred in diethylene glycol (24 mL) for 8 h at 135 °C. Potassium hydroxide (8.4 g) was added, which increased the temperature. A white solid condensed in the reflux condenser. The product was removed from the condenser with ether. The ether solution was dried with anhydrous Na_2SO_4 and solvent was removed under reduced pressure to yield **28** as a white solid (4.2 g, 78%); m.p. 99.0–100.0 °C. GC–MS: **28** 100%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.336 (d, 1 H), 1.442 (d, 1 H), 1.853 (m, 2 H), 1.909 (d, 1 H), 1.980 (s, 1 H), 2.043 (s, 1 H), 2.097 (m, 2 H), 2.191 (s, 2 H), 2.344 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.39, 34.35, 41.46 (secondary), 42.41, 43.72, 46.78, 47.79, 49.07, 51.64, 53.59 (tertiary), 76.59 (quaternary) ppm. GC–MS (τ = 8.334): *m*/*z* (%) = 80.10 (100), 79.05 (85.88), 114.10 (77.87), 77.15 (36.97), 66.10 (33.68).

If the crude chloro diketone **27** contains a significant admixture of chloro ketol **26**, the reaction mixture contains 1-chloro-*D*$_3$-trishomocubane-11-ol (**29**) after sublimation of alkyl chloride **28**. This chloro alcohol **29** was isolated by washing the reaction mixture with water and by extraction of product from the aqueous phase into chloroform. GC–MS (τ = 10.191): *m*/*z* (%) = 66.10 (100), 79.15 (89.47), 75.15 (83.12), 161.10 (65.75), 95.10 (62.01).

Supporting Information (see footnote on the first page of this article): Gaussian archive entries of the optimized structures; NMR spectra of new compounds.

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